Accepted Manuscript

A novel Barton decarboxylation produces a 1,4-phenyl radical rearrangement domino reaction

Alejandro Manchado, Mercedes García, Mateo M. Salgado, David Díez, Narciso M. Garrido

PII: S0040-4020(18)30578-7

DOI: 10.1016/j.tet.2018.05.043

Reference: TET 29550

To appear in: *Tetrahedron*

Received Date: 2 April 2018

Revised Date: 14 May 2018

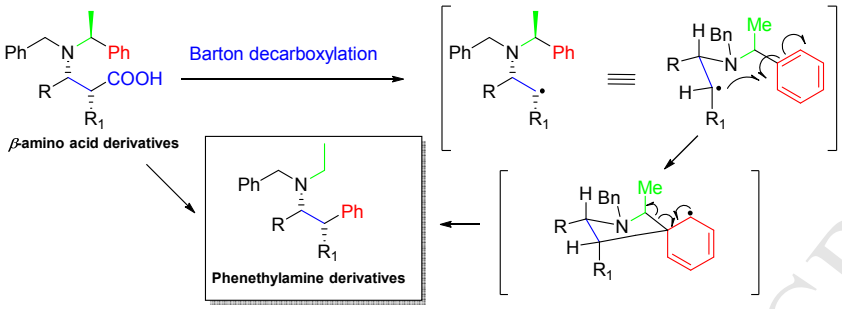
Accepted Date: 15 May 2018

Please cite this article as: Manchado A, García M, Salgado MM, Díez D, Garrido NM, A novel Barton decarboxylation produces a 1,4-phenyl radical rearrangement domino reaction, *Tetrahedron* (2018), doi: 10.1016/j.tet.2018.05.043.

Graphical Abstract

A novel Barton decarboxylation produces a 1,4-phenyl radical rearrangement domino reaction.

Alejandro Manchado, Mercedes García, Mateo M. Salgado, David Díez and Narciso M. Garrido.*



* Corresponding author. Tel.: +34-666589065; fax: +34-923-294574; e-mail: nmg@usal.es

A novel Barton decarboxylation produces a 1,4-phenyl radical rearrangement domino reaction.

Alejandro Manchado, Mercedes García, Mateo M. Salgado, David Díez and Narciso M. Garrido.∗

Dpto. de Química Orgánica, Facultad de Ciencias Químicas, Universidad de Salamanca, Plaza de los Caídos 1-5, 37008 Salamanca, Spain.

Dedicated to the memory of Professor Barton.

ABSTRACT

A novel 1,4-Phenyl radical rearrangement (1,4-PhRR) is described in a typical Barton decarboxylation procedure. While carrying out this reaction in presence of a *N*,*N*-disubstituted *β*-amino acid derivative, the decarboxyphenyl rearranged derivative is obtained, as well as in presence of *β*-*N*,*N*-acylamide. On the other hand, secondary amines give the *β*-lactam derivative without rearrangement, as well as *N*-Fmoc derivatives give the normal decarboxylation reaction. In regards of amines which are far away from the carboxylic group, such as *δ*-amino acid derivatives, the reaction occur through a typical Barton decarboxylation without rearrangement. The diversity of the reaction proves synthetic usefulness paving the way to interesting biologically active compounds.

KEYWORDS

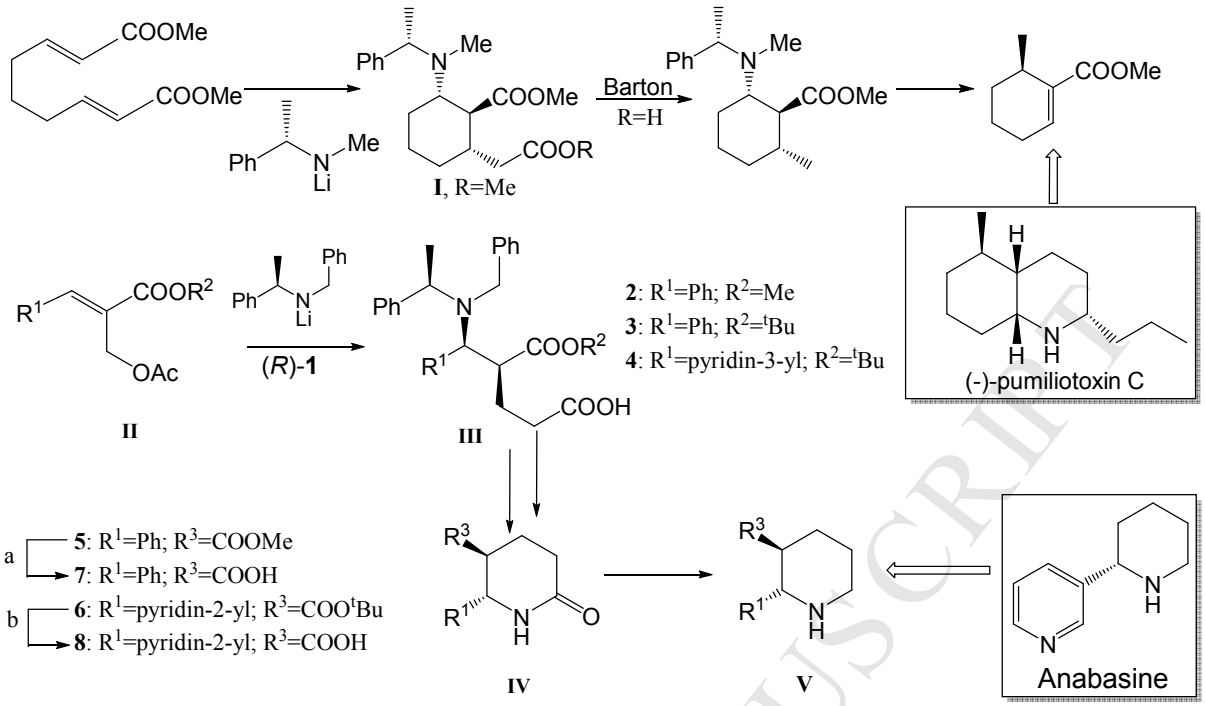
Barton decarboxylation, radical rearrangement, domino reaction, phenethylamine, amphetamine, ethamphetamine, adrenaline, ephedrine.

∗ Corresponding author. Tel.: +34-666589065; fax: +34-923-294574; e-mail: nmg@usal.es

1. Introduction

D.H.R. Barton has provided us with useful tools for organic synthesis, specially dealing with radical reaction since the discovery in 1960 of γ-functionalization using nitrite esters,[1] the radical deoxygenation known as Barton-McCombie reaction,[2] and the noteworthy decarboxylation reaction described first in collaboration with W.B. Motherwell and D. Crich[3] and then studied mechanistically with S.Z. Zard *et al.*[4] this reaction has been used several times by our group, especially with thiohydroxamic acids and it is the basic of this communication.

We have demonstrated two domino reactions by using chiral lithium amide with functionalized α,β-unsaturated esters: first when lithium (α-methylbenzyl)benzylamide (*R*)- or (*S*)-**1** is used to initiate the asymmetric conjugate addition cyclisation of nona-2,7-diendioate (scheme 1) to generate chiral cyclohexane derivatives **I**,[5] and applied it to the synthesis of (1*R*,5*R*,9*R*)-2-azabicyclo[3.3.1]nonane-9-carboxylic acid (morphanic acid),[5d] with a morphan scaffold, which was used in the synthesis of a new class of opioid receptor ligands.[5e] Importantly, the chemoselective hydrolysis of the acetic ester and further Barton decarboxylation pave the way to a formal synthesis of pumiliotoxin C.[5c,6] Second, a novel domino reaction: stereoselective Ireland-Claisen rearrangement and asymmetric Michael addition.[7] A protocol starting from Baylis-Hillman adducts **II** (Scheme 1) using chiral lithium amide (*R*)-**1** to afford δ-aminoacids **III**, that can be transformed to piperidones **IV** and further to piperidines **V**. When benzaldehyde was used as starting material in Baylis-Hillman reaction we have proved the application of the methodology toward the enantioselective synthesis of (+)-L-733,060 and (+)-CP-99,994.[7b] When cinnamaldehyde was used as starting material in Baylis-Hillman reaction, we have proved the application toward the synthesis of piperidinedicarboxylic acids (PDA)[7c] and actually our studies toward the synthesis of anabasine[8] required the use of the Barton decarboxylation reaction.



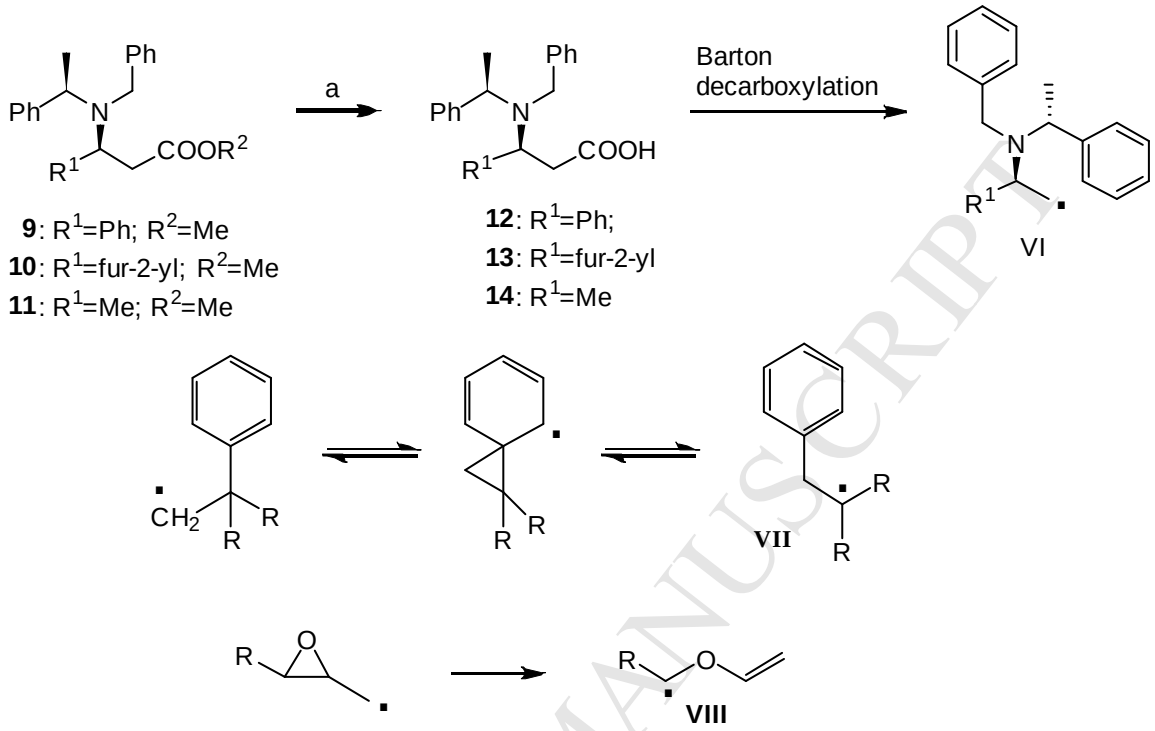
Scheme 1: Domino reactions: 1) With diendioate derivatives. 2) With Baylis-Hillman derivatives. Obtention of compounds **4**, **7** and **8**. Reagents and conditions: a) LiOH. b) TFA.

Phenethylamine-based drugs are a well-known family of compounds with highly and important bioactivity.[9] Small molecules such as adrenaline, noradrenaline, ephedrine or amphetamine and its derivatives have this kind of skeleton and they are used to treat neurologic disorders and mental issues, as they are neuronal central system stimulants.[10] Herein, we report the synthesis of phenethylamine derivatives bases on the discovery of a new domino reactions initiated in Barton decarboxylation from *β*-aminoacid derivatives followed by a 1,4-phenyl radical rearrangement (1,4-PhRR), which is a powerful tool in the synthesis of variety of these derivatives such as ethamphetamine[10], which is under study.

Results and discussion

As it has been reviewed recently by Davies et al., a great number of *β*-amino acids are accessible by asymmetric aza-Michael addition of chiral lithium amide to *α,β*-unsaturated esters,[11] alkaline hydrolysis provides the corresponding *N,N*-dibenzyldisubstituted amino acids in which we can anticipate a constrained environment for the incoming radical (**VI**) when performing Barton decarboxylation (scheme 2). The homobenzylic rearrangements indicated in the scheme 2 are known,[12] and usually take place when, in addition to regenerating the aromatic structure, a low

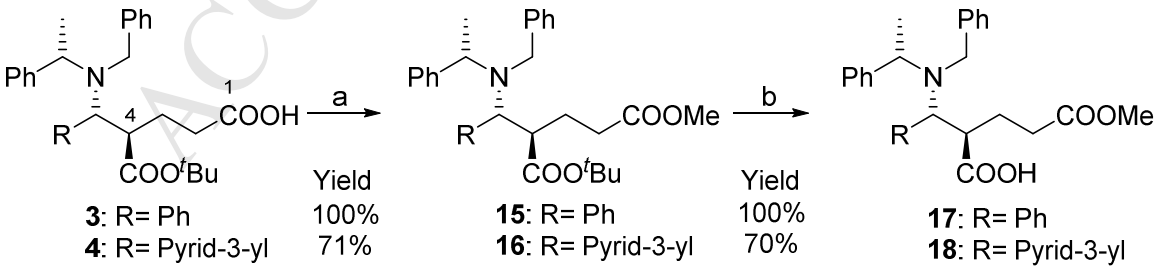
energy **VII** radical is obtained, or as when one of the R groups is an electron donor heteroatom, as it is indicated in the rearrangement of the radical epoxy described in scheme 2.



Scheme 2: Radical obtention proposal and known rearrangement. Reagents and conditions: a) LiOH.

The β-amino acids **12-14** were achieved by the aforementioned methodology and **2-4** by domino reaction to produce γ-aminoacid,[7] in this way we get to **7** and **8** (scheme 1). The rest of compounds that were treated under the mentioned reaction conditions were obtained as described below.

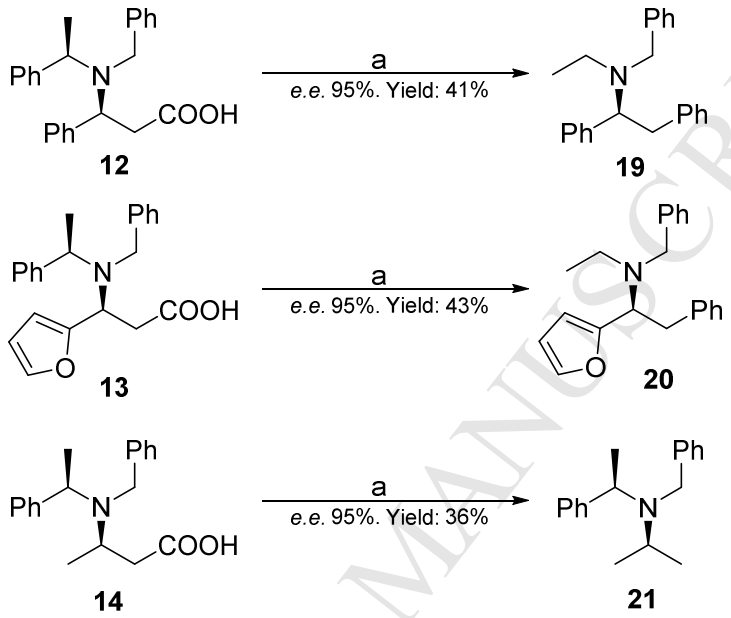
First of all, it is required a β-amino carboxyl derivative instead of δ-, for which the following reactions are carried out:



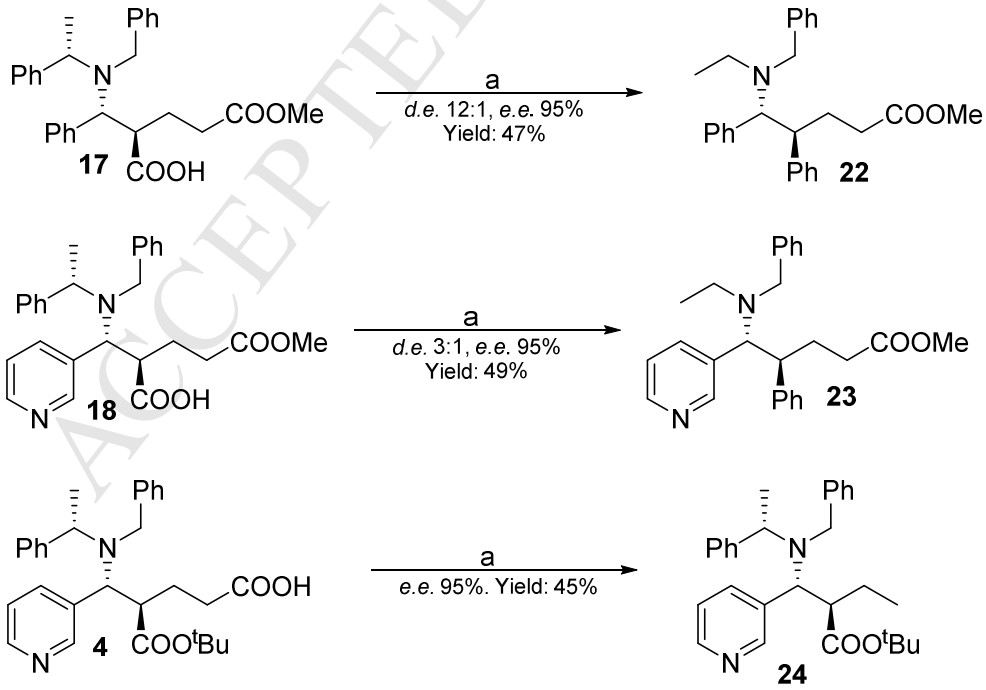
Scheme 3: Interchange of carboxy functionality. Reagents and conditions: a: Me_3SiCHN_2 2.0 M, C_6H_6/MeOH; b: TFA.

The treatment of **3** and **4** with Me_3SiCHN_2 leads to the diesters **15** and **16** with 100% and 70% yields respectively. The hydrolysis products **17** and **18** are obtained in 100% and 71% yield after treating the diesters with TFA.

With a variety of *β*-amino acids and *α*-alkyl-*β*-amino acids in hand the reactivity of Barton decarboxylation via thiohydroxamate esters was undertaken and the results are shown in scheme 4.



Reactivity of *β*-amino acid derivatives.



Reactivity of *α*-alkyl-*β*-amino acid and *δ*-amino acid derivatives.

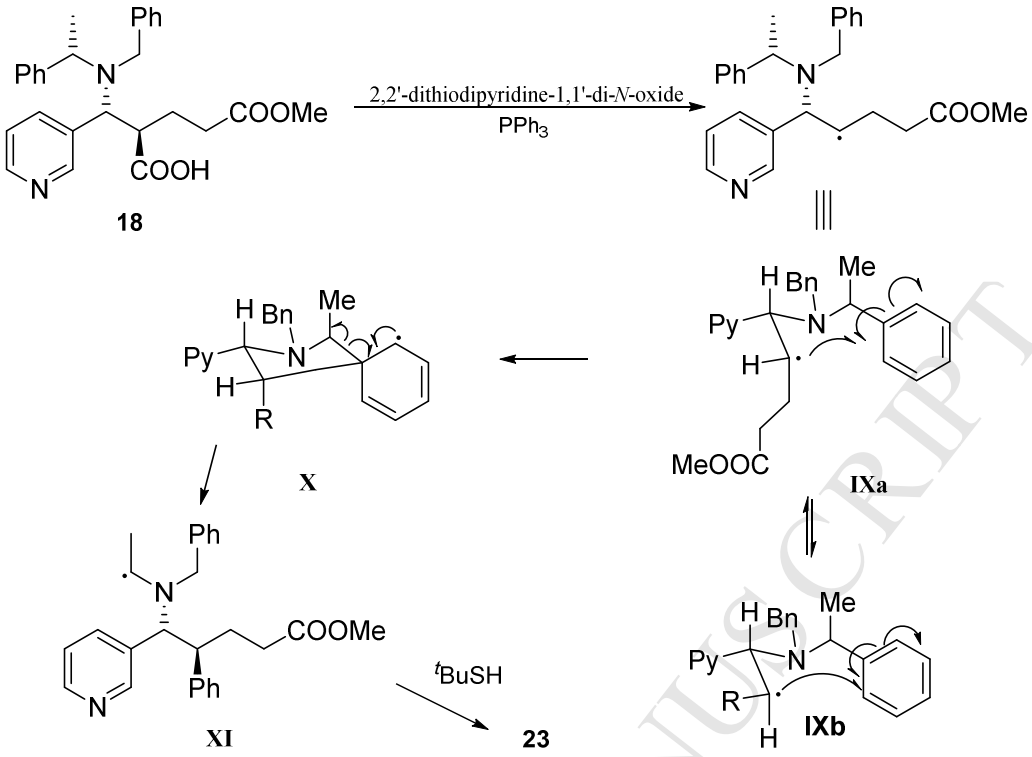
Scheme 4: Reactivity of amino acids. Reagents and conditions: a: 1) 2,2'-dithiodipyridine-1,1'-di-*N*-oxide, PPh_3, DCM. 2) *t*BuSH, h*v*.

The decarboxylation of **18** could produce a derivative that by hydrogenolysis would give the piperidone precursor of anabasine. However, when testing the decarboxylation on **18**, the expected reaction product is not obtained, but the rearranged compound **23** is obtained.

The spectroscopic data of **23** shows the existence of an ethyl group at δ ppm: 0.82 (3H, t, *J* = 6.9 Hz, NCH_2CH_3) and 2.55-2.64 (2H, m, NCH_2CH_3) and two unpaired methines at δ (ppm): 3.35 (1H, ddd, J = 11.3, 11.2 and 3.0 Hz, H-4) and 3.90 (1H, d, *J* = 11.0 Hz, H-5). In order to ascertain the structural complexity two-dimensional normal heteronuclear (HMQC) and long-range correlation (HMBC) experiments corroborate the structure of **23** and allow the assignment of all its spectroscopic data. The conectivities of C_{ipso} of phenyl on C-4 with *H*-5 and *H*-4 that fix its position and those of CH_2 (of ethyl) with CH_2Ph and with *H*-5 stand out.

Thus, a radical benzylic rearrangement is described in which a 1,4 migration of phenyl occurs and which is unprecedented in the literature.

In our case, the proposed reaction mechanism is the one indicated in scheme 5, in which the radical, which initially formed **IX**, evolves due to the proximity of the aromatic ring, in analogy with the homobenzylic rearrangement described, giving the radical with the spiranic carbon **X** that evolves immediately to produce the low energy intermediate **XI** due to the existence of nitrogen as an electron donor, which in the presence of the hydrogen donor (*t*BuSH) generates the final product of reaction.

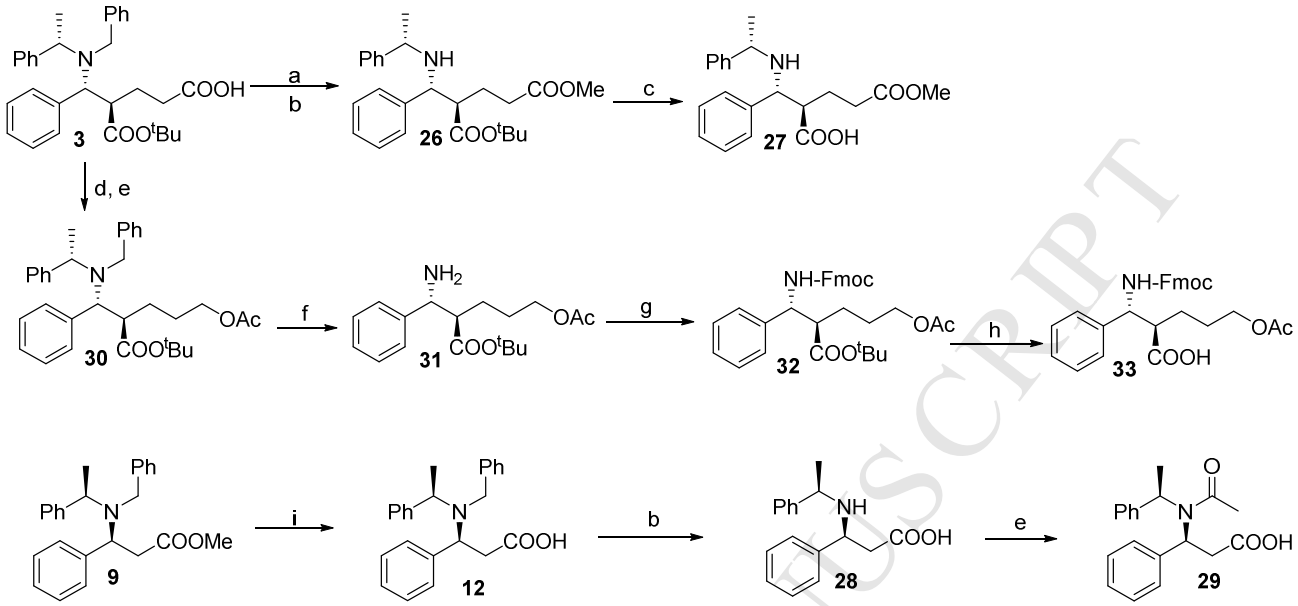


Scheme 5: Proposed mechanism for 1,4-phenyl radical rearrangement.

Given the unexpected result, the reaction was carried out several times, always obtaining the same result. The loss of stereoselectivity found in C-4 could be due to inversion of radical configuration from **IXa** to **IXb**, shown in scheme 5. Similar retention of configuration is account by Walborsky *et al.*[13] in cycloprpyl radical system by Barton decarboxylation reaction with a level of retention till 84% using *tert*-butylthiol as the hydrogen donating reagent, and by Buckmelter *et al.*[14] by enantioselective decarboxylation in tetrahydropyran core with different hydrogen atom donors (*tert*-butylthiol included).

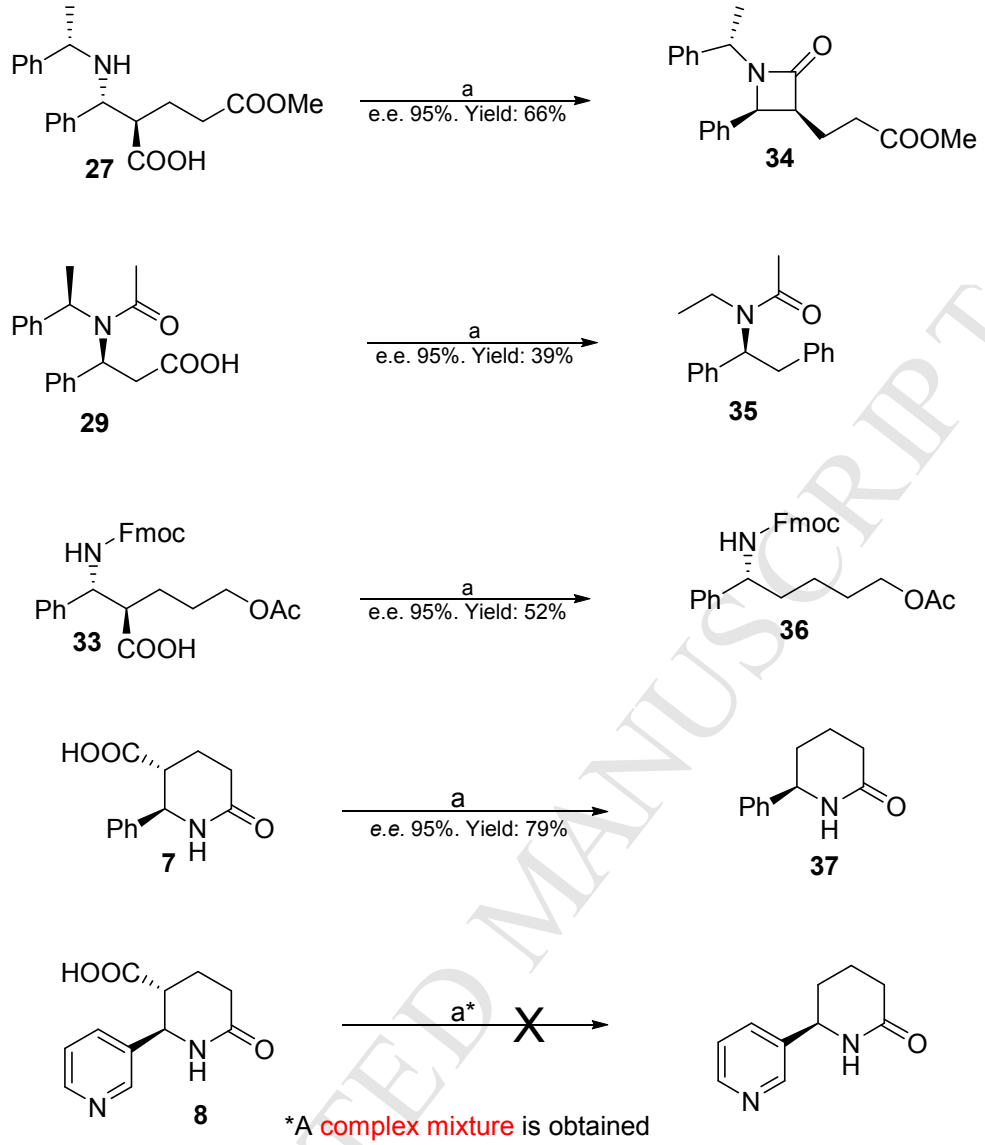
Phenyl derivative **17** behave in the same way but with better selectivity (12:1), β-amino acids **12** and **13** produce 1,4-PhRR derivatives **19** and **20** with 41% and 43% yields respectively. But, when the carboxyl is δ to the amine group, the radical is far away from the phenyl group and the decarboxylation compound **24** is obtained, as well as when methyl derivative **14** is treated under same conditions yielding **21**, probably by a less steric demanding environment or probably the reaction needs more time under radical mediation, as could be by using a slower hydrogen atom donor such as *n*-Bu_3SnH, 1,4-cyclohadiene, Ph_3SiH or Et_3SiH.[15] Computational and kinetic studies are underway to control this reactivity.

In order to amplify the scope of the reaction we get some new β-amino acid such as **27**, **29** and **33** as shown in scheme 6, and the cyclic β-amino acids **7** and **8** in scheme 1.



Scheme 6: Reagent and conditions: a: Me_3SiCHN_2, C_6H_6/MeOH. b: CAN, MeCN/H_2O. c: TFA. d: BH_3, THF. e: Ac_2O, pyr. f: H_2, Pd/C, AcOH. g: $NaHCO_3$/Fmoc-OSu, Acetone/H_2O. h: TFA. i: LiOH, MeOH/THF/H_2O.

In scheme 7 it is shown the results of performing Barton decarboxylation with these compounds.



a: 1) 2,2'-dithiodipyridine-1,1'-di-*N*-oxide, PPh_3, DCM. 2) *t*BuSH, h*v*

Scheme 7: Reactivity of modified amines, and piperidone carboxylic acids. Reagents and conditions: a: 1) 2,2'-dithiodipyridine-1,1'-di-*N*-oxide, PPh_3, DCM. 2) *t*BuSH, hν.

N-*α*-methylbenzyl and *N*-acetyl amide **29** gives way to compound **35** through the 1,4-PhRR, in which decarboxylation was established by MS and the structure by two-dimensional NMR experiments ($^1H/^1H$ and $^1H/^{13}C$, SI) showing the existence of rotamers. On the other hand, *N*-*α*-methylbenzyl secondary amine under the same condition provides *β*-lactam **34**, as a conveniet method for activation of carboxyl group toward cyclic amide formation, HNFmoc derivative **33** provides decarboxylation showing an alternative way to obtained anabasine and his phenyl homologue. *N*-debenzylation of **19** and **20** will provide aromatic homologues of ethamphetamine. From these results it could be assess that tertiary *β*-amine or *β*-amide acids with an aromatic *β*-substituent under Barton decarboxylation will provide the 1,4-PhRR described. It is probably that *π*-

stacking interaction within **IXa** in scheme 5 favors the appropriate configuration for the rearrangement. With *β*-alkyl substituent only decarboxylation has been observed and further studies are needed to retard the donation of the hydrogen atom. Other compounds devoid of the proximity of dibenzylamine give rise to usual decarboxylation.

Further work is overtaken in our laboratory to obtain the pharmacological active compound as well as to perform SAR studies.

Conclusions

D.H.R. Barton has provided us with tools for diversity in this way by using his typical procedure for decarboxylation. We can achieve it properly in compounds such as **4**, **7**, **14** and **33** to provide **24**, **21**, **37** and **36** respectively. Nevertheless, when we treat in this condition secondary derivative **27**, we obtain *β*-lactam **34** by carboxyl activation, and, interestingly, when *β*-amino acid **10** and **11** or *α*-alkyl-*β*-amino acids **17** and **18** were treated under the same condition we got **20**, **21**, **22** and **23** respectively via an unknown 1,4-phenyl radical rearrangement that we described for the first time.

This gives way to provide in one pot procedure a domino process by radical decarboxylation followed by 1,4-phenyl radical rearrangement to provide from *β*-amino acids derivatives phenethylamines, interesting class of pharmaceutical derivatives from which ethamphetamine and related compounds is a future objective.

Experimental

All chemical reagents were purchased from Sigma-Aldrich or Acros. High-purity reaction solvents were purified accordingly to literature. All reactions were carried out in borosilicate Pyrex® type glassware and under inert conditions, using Ar as inert gas. Reaction monitoring was followed by TLC, type Merck 60 F254, which visualization was achieved with UV light and ninhydrin or potassium permanganate as appropriate stains. Flash chromatography was carried out on Kieselgel 40 (Merck, 0.040-0.063) silica. Yields and characterization data belong to chromatography purified compounds. Deuterated solvents were purchased from Carlo Erba. Optical rotations were measured on a Perkin Elmer 241 polarimeter in 1 dm cells ($[\alpha]_D^{20}$). Infrared spectra were recorded on a Shimadzu IRAffinity-1 (IR). NMR experiments were recorded on a Varian 200 VX (^{1}H NMR/200 MHz, ^{13}C NMR/50 MHz) and on a Bruker DRX 400 (^{1}H NMR/400 MHz). 2D HMBC, HMQC or representative compounds were also recorded to assign protons and carbons on new structures. 2D COSY ^{1}H-^{1}H homonuclear correlations have been determined by ^{1}H-^{1}H COSY experiment with double function filler and gradients on a Bruker DRX 400. 2D HSQC ^{1}H-^{13}C heteronuclear

correlations have been determined by ^{1}H-^{13}C HSQC experiment with single quantum filler and gradients, also on a Bruker DRX 400. Chemical shifts are reported in ppm (parts per million) relative to referenced values. High-resolution mass spectrometry (HRMS) analyses were performed on an Applied Biosystems QSTAR XL (ESI, electrospray ionization) and in a VG-TS 250 (EI, electronic impact), at 70 eV (m/z).

The compounds 12, 13, 14,[11], 7[7c] and 17, 18[7a] were prepared according to the cited references.

General Barton decarboxylation procedure

The suitable substrate is dissolved in DCM. In a dark room, as the Barton reagent is photosensitive, 1 equivalent of 2,2'-dithiodipyridine-1,1'-di-*N*-oxide (Barton reagent) is added, as same as 1 equivalent of triphenylphosphine. In constant agitation, the reaction is carried out in darkness conditions.

Once the reaction finished, 3 equivalents of *tert*-butylthiol are added and the mixture is irradiated with two 220 W lights.

After an hour, all the solvent is evaporated and the reaction product is chromatographed.

(*S*)-*N*-benzyl-*N*-ethyl-1,2-diphenylethan-1-amine (**19**)

Following the general Barton decarboxylation procedure, the reaction was carried out with 70 mg of **9** (0.20 mmol), 52 mg of triphenylphosphine (0.20 mmol) and 50 mg of 2,2'-dithiodipyridine-1,1'-di-*N*-oxide (0.20 mmol). After stirring the reaction for 3 hours, 0.07 mL of *tert*-butylthiol (0.60 mmol) were added and after irradiation the mixture for 1 hour the product were isolated with hex:EtAcO 99:1. In the end, 20 mg were obtained. Yield: 31%.
$[\alpha]_D^{26}$= -5.4 (*c* 0.53, $CHCl_3$) **NMR ^{1}H** δ (ppm) (200 MHz, $CDCl_3$): 1.05 (3H, t, *J*= 7.10 Hz, NCH_2CH_3), 2.2-2.4 (1H, dq, *J*= 13.0 and 6.95 Hz, NCH_AHCH_3), 2.65-2.83 (1H, dq, *J*= 13.0 and 6.95 Hz, $NCHH_BCH_3$), 2.93-3.07 (1H, m, $PhCH_AH$), 3.22-3.35 (1H, AB, J_{AB}= 14.33, NCH_AHPh), 3.3-3.38 (1H, m, $PhCHH_B$), 3.75-3.85 (1H, d, J_{AB}= 14.33, $NCHH_BPh$), 4.00 (1H, t, *J*= 7.42, PhCH), 7.02-7.51 (15H, m, ArH). **NMR ^{13}C** δ (ppm) (50 MHz, $CDCl_3$): 29.72 (CH_3, NCH_2CH_3), 38.30 (CH_2, NCH_2CH_3), 43.13 (CH_2, C-2), 53.94 (CH_2, NCH_2Ph), 64.99 (CH, C-1), 127-129.4 (Cx15, Ar), 139.95-142.5 (Cx3, C_{ipso}).

(*S*)-*N*-benzyl-*N*-ethyl-1-(furan-2-yl)-2-phenylethan-1-amine (**20**)

The general procedure was followed and the next reagent amounts were added: 88 mg of **10** (0.25 mmol), 66 mg of triphenylphosphine (0.25 mmol) and 63 mg of 2,2'-dithiodipyridine-1,1'-di-*N*-oxide (0.25 mmol). The reaction was stirred for 4 hours and then 0.085 mL of *tert*-butylthiol (0.75 mmol) were added and, after 1 hour, the product mixture was chromatographed. In the end, 9 mg of **20** were obtained after eluting with hex:EtAcO 99:1. Yield: 33% .

$[\alpha]_D^{26}$= -44.7 (*c* 0.30, $CHCl_3$). **NMR ^{1}H** δ (ppm) (200 MHz, $CDCl_3$): 0.99 (3H, t, *J* = 7.1 Hz, NCH_2CH_3), 2.28 (1H, dq, *J*= 13.5 and 6.8 Hz, NCH_AHCH_3), 2.84 (1H, dq, *J*= 13.5 and 6.8 Hz, $NCHH_BCH_3$), 3.14 (2H, d, *J*= 7.6 Hz, CH_2, C-2), 3.29 (1H, d, *J*= 14.3 Hz, NCH_AHPh), 3.89 (1H, d, *J*= 14.3 Hz, $NCHH_BPh$), 4.02 (1H, t, *J*= 7.6 Hz, CH, C-1), 6.35 – 6.05 (3H, m, CH, Fur), 7.66 – 6.89 (10H, m, ArH). **NMR ^{13}C** δ (ppm) (50 MHz, $CDCl_3$): 13.61 (CH_3, NCH_2CH_3), 37.57 (CH_2, NCH_2CH_3), 44.07 (CH_2, C-2), 54.59 (CH_2, NCH_2Ph), 58.49 (CH, C-1), 106.28-109.67 (CH, Fur), 125.84-130.05 (CHx10, Ph), 139.67-141.43 (Cx3, C_{ipso}). **IR** ν_{max} (cm^{-1}): 2964, 2926, 2852, 737, 698.

<u>*N*-benzyl-*N*-ethylpropan-2-amine (**21**)</u>

The next quantities were added following the general procedure: 22 mg of **11** (0.07 mmol), 20 mg of triphenylphosphine (0.07 mmol) and 19 mg of 2,2'-dithiodipyridine-1,1'-di-*N*-oxide (0.07 mmol). After 4 hours, 0.025 mL of *tert*-butylthiol were added and after 1 hour, the product mixture was chromatographed. In the end, 5 mg of **21** was obtained with hex:EtAcO 99:1. Yield: 26%.

NMR ^{1}H δ (ppm) (200 MHz, $CDCl_3$): 0.91 (6H, d, *J*= 6.6 Hz, $CH(CH_3)_2$), 1.05 (3H, d, *J*= 6.6 Hz, $NCHCH_3$), 3.00 (1H, quint, *J*= 6.6 Hz, $CH(CH_3)_2$), 3.70 (2H, AB, J_{AB}= 15.4 Hz, NCH_2Ph), 3.91 (1H, q, *J*= 6.6 Hz, $NCHCH_3$), 7.91 – 7.00 (10H, m, ArH).

<u>Methyl (4*S*,5*R*)-5-(benzyl(ethyl)amino)-4,5-diphenylpentanoate (**22**)</u>

Following Barton decarboxylation procedure, the next quantities were added: 91 mg of **17** (0.20 mmol), 63 mg of triphenylphosphine (0.23 mmol) and 60 mg of 2,2'-dithiodipyridine-1,1'-di-*N*-oxide (0.20 mmol). After 4 hours of reaction, 0.070 mL of *tert*-butylthiol (0.60 mmol) were added and the mixture was irradiated for 90 minutes. After eluting the product mixture with hex:EtAcO 99:1, 29 mg of **22** were obtained. Yield: 37%.

$[\alpha]_D^{26}$= +33.2 (*c* 1.44, $CHCl_3$). **NMR ^{1}H** δ (ppm) (400 MHz, $CDCl_3$): 0.81 (3H, t, *J*= 6.9 Hz, NCH_2CH_3), 1.54-1.62 (1H, m, H-3_B), 1.67-1.74 (2H, m, H-2), 1.98-2.04 (2H, m, NCH_2CH_3), 2.53-2.58 (1H, m, H-3_A), 2.92 (1H, AB, J_{AB}= 14 Hz, NCH_AHPh), 3.34 (1H, dt, *J*= 11.0 and 3.6 Hz, H-4), 3.51 (3H, s, $COOCH_3$), 3.75 (1H, AB, J_{AB}= 14.0 Hz, $NCHH_BPh$), 3.88 (1H, d, *J*= 11.1 Hz, H-5), 7.00-7.46 (15H, m, ArH). **NMR ^{13}C** δ (ppm) (50 MHz, $CDCl_3$): 13.3 (CH3, NCH_2CH_3), 29.6 (CH_2,

C-3), 32.4 (CH_2, C-2), 42.9 (CH_2, NCH_2CH_3), 47.2 (CH, C-4), 51.5 (CH_3, $COOCH_3$), 53.6 (CH_2, NCH_2Ph), 67.9 (CH, C-5), 126.4-129.3 (CHx15, Ar), 137.2 (C, C_{ipso}), 140.5 (C, C_{ipso}, CHPh), 142.7 (C, C_{ipso}, CH_2Ph), 174.1 (C, $COOCH_3$). **IR** ν_{max} (cm^{-1}): 3394, 3059, 3026, 2922, 2804, 1736, 1488, 1452, 1365, 1156, 1073, 753, 700. **H.R.M.S.**, FAB, calcd for $C_{27}H_{32}O_2N$ $[M+H]^+$: 402.2427, found: 402,2423.

Methyl (4*S*,5*R*)-5-(benzyl(ethyl)amino)-4-phenyl-5-(pyridin-3-yl)pentanoate (**23**)

Following the Barton decarboxylation procedure, the reaction was carried out with these reagent quantities: 100 mg of **18** (0.22 mmol), 69 mg of triphenylphosphine (0.26 mmol) and 67 mg of 2,2'-dithiodipyridine-1,1'-di-*N*-oxide (0.26 mmol). After 3 hours, 0.074 mL of t*ert*-butylthiol (0.66 mmol) were added and the reaction mixture irradiated for 50 minutes. After the reaction product was chromatographed, 34 mg of **23** were obtained when eluting with hex:EtAcO 9:1. Yield: 39%.
$[\alpha]_D^{26}$= +11.3 (*c* 1.21, $CHCl_3$). **NMR ^{1}H** δ (ppm) (400 MHz, $CDCl_3$): 0.82 (3H, t, *J*= 6.9 Hz, NCH_2CH_3), 1.48-1.57 (1H, m, H-3_B), 1.59-1.68 (1H, m, H-3_A), 1.99-2.02 (2H, m, H-2), 2.55-2.64 (2H, m, NCH_2CH_3), 2.87 (1H, AB, J_{AB}= 14.0 Hz, NCH_AHPh), 3.35 (1H, ddd, *J*= 11.3, 11.2 and 3.0 Hz, H-4), 3.52 (3H, s, $COOCH_3$), 3.74 (1H, AB, J_{AB}= 14.0 Hz, $NCHH_BPh$), 3.90 (1H, d, *J*=11.0 Hz, H-5), 7.06-7.31 (10H, m, ArH), 7.56 (1H, d, *J*= 8.4 Hz, H-5-pyr), 8.46 (1H, d, *J*= 3.4 Hz, H-4-pyr), 8.54 (2H, s, *J*= 3.4 Hz, H-2-pyr and H-6-pyr). **NMR ^{13}C** δ (ppm) (50 MHz, $CDCl_3$): 13.2 (CH_3, NCH_2CH_3), 29.3 (CH_2, C-3), 32.0 (CH_2, C-2), 42.8 (CH_2, NCH_2CH_3), 46.5 (CH, C-4), 51.7 (CH_3, $COOCH_3$), 53.6 (CH_2, NCH_2Ph), 65.7 (CH, C-5), 126-128.9 (CHx10, Ar), 136.3 (C, C-3-pyr), 139.7 (C, C_{ipso}, CH_2Ph), 141.9 (C, C_{ipso}, CHPh), 173.9 (C, $COOCH_3$). **IR** ν_{max} (cm^{-1}): 3060, 3027, 2930, 2847, 2800, 1736, 1452, 1425, 1365, 1211, 1166, 1026, 700. **H.R.M.S.**, FAB, calcd for $C_{26}H_{31}O_2N_2$ $[M+H]^+$: 402.2427, found: 102, 2423

Tert-butyl (*S*)-2-((*S*)-(benzyl((*R*)-1-phenylethyl)amino)(pyridin-3-yl)methyl)butanoate (**24**)

After following the general procedure and adding 50 mg of **4** (0.10 mmol), 31 mg of triphenylphosphine (0.10 mmol) and 30 mg of 2,2'-dithiodipyridine-1,1'-di-*N*-oxide (0.11 mmol), the reaction was stirred for 5 hours and, then, 0.034 ml of *tert*-butylthiol (0.30 mmol) were added. After irradiating the mixture for 50 minutes, the reaction crude was chromatographed and the desired product isolated with hex:EtAcO 8:2. In the end, 20 mg of **24** were obtained. Yield: 35%.
$[\alpha]_D^{26}$= +37.9 (*c* 1.33, $CHCl_3$). **NMR ^{1}H** δ (ppm) (400 MHz, $CDCl_3$): 0.81 (3H, t, *J*= 7.5 Hz, CH_2CH_3), 0.98 (3H, d, *J*=6.8 Hz, $NCHCH_3$), 1.01 (9H, s, $C(CH_3)_3$), 2.10-2.16 (2H, m, CH_2CH_3), 2.86 (1H, dt, *J*= 11.6 and 3.6 Hz, H-2), 3.58 (1H, AB, J_{AB}= 13.8 Hz, NCH_AHPh), 3.87 (1H, d, *J*=

11.6 Hz, H-3), 4.00 (1H, AB, J_{AB}= 13.8 Hz, NHH_BPh), 4.13 (1H, q, *J*= 6.8 Hz, $NCHCH_3$), 7.23-7.37 (10H, m, ArH), 7.56 (1H, d, *J*= 8.4 Hz, H-5-pyr), 8.46 (1H, d, *J*= 3.4 Hz, H-4-pyr), 8.54 (2H, s, *J*= 3.4 Hz, H-2-pyr and H-6-pyr). **NMR ^{13}C** δ (ppm) (50 MHz, $CDCl_3$): 11.9 (CH_3, CH_2CH_3), 15.0 (CH_3, C(α)Me), 24.0 (CH_2, CH_2CH_3), 27.7 (CH_3x3, $C(CH_3)_3$), 50.8 (CH_2, $NNCH_2Ph$), 51.7 (CH, C-2), 56.1 (CH, C(α)), 60.9 (CH, C-3), 80.5 (C, $C(CH_3)_3$), 123.3 (CH, C-5-pyr), 127.2-129.2 (CHx10, Ar), 136.8 (C, C-3-pyr), 137.2 (CH, C-4-pyr), 139.8 (C, C_{ipso}, CH2Ph), 177.0 (C, C_{ipso}, CHPh), 148.3 (CH, C-6-pyr), 150.4 (CH, C-2-pyr), 173.5 (C, COO^tBu). **IR** ν_{max} (cm^{-1}): 3031, 2971, 2933, 2875, 1724, 1446, 1370, 1261, 1158, 1073, 936, 700. **H.R.M.S.**, FAB, calcd for $C_{29}H_{37}O_2N_2$ $[M+H]^+$: 445.2855, found: 445,2883.

Methyl 3-((3*S*,4*S*)-2-oxo-4-phenyl-1-((*S*)-1-phenylethyl)azetidin-3-yl)propanoate (**34**)

The following reagent amounts were added using the general Barton decarboxylation procedure: 20 mg of **27** (0.06 mmol), 19 mg of triphenylphosphine (0.06 mmol) and 17 mg of 2,2'-dithiodipyridine-1,1'-di-*N*-oxide (0.06 mmol). After 5 hours of reaction, 0.020 mL of *tert*-butylthiol (0.18 mmol) were added and after 1 hour of irradiation, the product mixture was chromatographed and the desired product was eluted with hex:EtAcO 8:2. Yield: 66%.

$[\alpha]_D^{26}$= +103.3 (*c* 0.96, $CHCl_3$). **NMR ^{1}H** δ (ppm) (400 MHz, $CDCl_3$): 1.36-1.41 (1H, m, H-1'$_B$), 1.43 (3H, d, *J*= 7.2 Hz, $NCHCH_3$), 1.74-1.82(1H, m, H-1'$_A$), 2.13-2.20 (2H, m, H-2'), 3.31 (1H, q, *J*= 5.6 Hz, H-3), 3.57 (3H, s, $COOCH_3$), 4.52 (1H, d, *J*= 5.6 Hz, H-4), 4.98 (1H, q, *J*= 7.2 Hz, $NCHCH_3$). 7.23-7.34 (10H, m, ArH). **NMR ^{13}C** δ (ppm) (50 MHz, $CDCl_3$): 19.6 (CH_3, C(α)Me), 21.1 (CH_2, C-1'), 31.4 (CH_2, C-2'), 51.8 (CH_3, $COOCH_3$), 52.8 (CH, C-4), 53.6 (CH, C-3), 58.0 (CH, C(α)), 127.5-129.9 (CHx10, Ar), 136.8 (C, C_{ipso}, CHPh), 140.4 (C, C_{ipso}, CHPh), 170.6 (C, $COOCH_3$), 173.4 (C, C-2). **IR** ν_{max} (cm^{-1}): 3031, 2951, 1743, 1495, 1455, 1376, 1200, 1026, 700. **H.R.M.S.**, FAB, calcd for $C_{21}H_{24}O_3N$ $[M+H]^+$: 338.1751, found: 338.1730.

(*S*)-*N*-(1,2-diphenylethyl)-*N*-ethylacetamide (**35**)

Following the general Barton decarboxylation procedure, the next quantities were added: 25 mg of **29** (0.08 mmol), 21 mg of triphenylphosphine (0.08 mmol) and 20 mg of 2,2'-dithiodipyridine-1,1'-di-*N*-oxide (0.08 mmol). After 3 hours, 0.030 mL of *tert*-butylthiol (0.24 mmol) were added and after 50 minutes of irradiation, the product mixture was chromatographed and 5 mg of the desired product was isolated with a elution of hex:EtAcO 8:2. A rotamer mixture ^{1}H RMN spectra was found. Yield: 39%.

NMR ^{1}H δ (ppm) (400 MHz, $CDCl_3$): Rotamer A: 0.76-0.82 (3H, m, CH_3CH_2N), 1.76 (3H, s, CH_3CO), 3.10-3.18 (1H, AB, J_{AB}=6.8 Hz, $CH_3CH_AH_BN$), 3.30-3.34 (2H, m, $PhCHCH_2Ph$), 3.49-3.54 (1H, AB, J_{AB}=6.7 Hz, $CH_3CH_AH_BN$), 5.10-5.14 (1H, m, PhCH), 7.2-7.4 (10H, m, ArH). Rotamer B: 0.75-0.81 (3H, m, CH_3CH_2N), 1.9 (3H, s, CH_3CO), 3.17-3.23 (2H, m, CH_3CH_2N), 3.35-3.37 (2H, d, J=7.9 Hz $PhCHCH_2Ph$), 6.1-6.14 (1H, t, J=7.9 Hz, $PhCHCH_2Ph$), 7.2-7.4 (10H, m, ArH) **NMR ^{13}C** δ (ppm) (50 MHz, $CDCl_3$): Rotamer A: 13.7 (CH_3, CH_3CH_2N), 22.6 (CH_3, CH_3CO), 36.7 (CH_2, CH_3CH_2N), 37.3 (CH_2, $PhCHCH_2Ph$), 57.2 (CH, NCHPh), 126.3-129.2 (CH, Ar), 138.3 (Cx2, C_{ipso}), 170.7 (C, CO). Rotamer B: 13.7 (CH3, CH_3CH_2N), 22.6 (CH_3, CH_3CO), 37.2 (CH_2, CH_3CH_2N), 39.8 (CH_2, $PhCHCH_2Ph$), 63.2 (CH, NCHPh), 126.3-129.2 (CH, Ar), 139.9 (Cx2, C_{ipso}), 170.7 (C, CO). **H.R.M.S.**, FAB, calcd for $C_{18}H_{22}ON$ $[M+H]^+$: 268.1696, found: 268.1704.

(*R*)-5-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-phenylpentyl acetate (**36**)

Barton decarboxylation procedure was followed and 14 mg of **33** (0.04 mmol), 11 mg of triphenylphosphine (0.04 mmol) and 10 mg of 2,2'-dithiodipyridine-1,1'-di-*N*-oxide (0.04 mmol) were added and the reaction was carried out for 3 hours. Then, 0.012 mL of *tert*-butylthiol were added and the reaction was irradiated for 1 hour. The desired product was isolated after a chromatography by eluting with hex:EtAcO 9:1 and 8 mg were obtained. Yield 52%.
$[\alpha]_D^{26}$= +18.8 (*c* 0.58, $CHCl_3$). **NMR ^{13}C** δ (ppm) (50 MHz, $CDCl_3$): 22.8 (CH_3, $OCOCH_3$), 21.2 (CH_2, C-3), 28.5 (CH_2, C-2), 36.3 (CH_2, C-4)47.5 (CH, Fmoc), 55.5 (CH, C-5), 64.3 (CH_2, C-1), 66.7 (CH_2, CH_2Fmoc), 120.2-129.0 (CHx13, Ar), 139.8 (C, C_{ipso}), 141.5 (Cx2, $C_{ipsoFmoc}$), 144.1 (Cx2, $C_{ipsoFmoc}$), 156.0 (C, NHCO), 171.4 (C, $OCOCH_3$). **IR** ν_{max} (cm^{-1}): 3336, 3063, 3031, 2948, 2862, 1734, 1533, 1450, 1367, 1243, 1089, 1030, 759, 741.

(*R*)-6-phenylpiperidin-2-one (**37**)

General Barton procedure was carried out with 29 mg of **7** (0.13 mmol), 41 mg of triphenylphosphine (0.16 mmol) and 39 mg of 2,2'-dithiodipyridine-1,1'-di-*N*-oxide (0.15 mmol). After 90 minutes 0.044 mL of *tert*-butylthiol were added and the solution was irradiated for 1 hour. After chromatographed, 18 mg of **37** were obtained while eluting with hex:EtAcO 1:1. Yield: 79%.
$[\alpha]_D^{26}$= +34.2 (*c* 0.68, $CHCl_3$). **NMR ^{1}H** δ (ppm) (400 MHz, $CDCl_3$): 1.68 (1H, m), 1.80 (1H, m), 1.90 (1H, m), 2.11 (1H, m), 2.43-2.54 (2H, m, H-5), 4.55 (1H, m, H-6), 5.97 (1H, s, NH), 7.25-7.37 (5H, m, ArH). **NMR ^{13}C** δ (ppm) (50 MHz, $CDCl_3$): 19.9 (CH_2, C-4), 31.5 (CH_2, C-5), 32.3 (CH_2, C-3), 58.0 (CH, C-6), 126.3-129.1 (CHx5, Ar), 142.7 (C, C_{ipso}), 172.7 (C, C-2). **IR** ν_{max} (cm^{-1}): 3228,

2926, 2854, 1654, 1457, 1406, 1340, 1302, 700. **H.R.M.S.**, FAB, calcd for $C_{11}H_{14}ON$ $[M+H]^+$: 176.1075, found: 176.1058.

(*R*)-6-(pyridin-3-yl)piperidin-2-one

Following the general Barton decarboxylation procedure, the reaction was carried out with 40 mg of **8** (0.18 mmol), 57 mg of triphenylphosphine (0.22 mmol) and 54 mg of 2,2'-dithiodipyridine-1,1'-di-*N*-oxide (0.22 mmol). After 22 hours, 0.06 mL of *tert*-butylthiol (0.54 mmol) were added and the mixture was irradiated with two 220 W lights for 90 minutes. The solvent was removed and, after the mixture was chromatographed, no desired product was isolated.

Acknowledgments

The authors are grateful for financial support from MINECO CTQ2015-68175-R, FEDER Junta de Castilla y León (UIC21) and Junta de Castilla y León, (SA162A12-1). The authors also thank Dr. A. M. Lithgow for work on the NMR spectra and Dr. César Raposo for the Mass spectra and X-ray diffraction service of the NUCLEUS platform of the University of Salamanca. C.T.N. thanks Junta de Castilla y León for a FPI predoctoral fellowship.

Supplementary Material

Supplementary material that may be helpful in the review.

References and notes

1. D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Am. Chem. Soc.* **1960**, *82*, 2640-2641.

2. a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

b) McCombie, S. W.; Motherwell, W. B.; Tozer, M. *Org. React.* **2011**, *77*, 161.

3. a) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1983**, 939-941.

b) Barton, D. H. R.; Crich, D.; Motherwell, W. B., *Tetrahedron Lett.*, **1983**, 24, 4979.

c) Barton, *D. H. R.*; Crich, D.; Motherwell, W. B., *Tetrahedron Lett.*, **1985**, *41*, 3901.

d) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901-3924.

4. a) Barton, D. H. R.; Bridon, D.; Zard, S. Z.; Fernandaz-Picot, I., *Tetrahedron.* **1987**, *43*, 2733.

b) Barton, D. H. R.; Zard, S. Z. *Pure Appl. Chem.* **1986**, *58*, 675-684.

5. a) Urones, J. G.; Garrido, N. M.; Díez, D.; Dominguez, S. H.; Davies, S. G. *Tetrahedron: Asymmetry* **1999**, *10*, 1637-1641.

b) Davies, S. G.; Diez, D.; Dominguez, S. H.; Garrido, N. M.; Kruchinin, D.; Price, P. D.; Smith, A. D. *Org. Biomol. Chem.* **2005**, *3*, 1284-1301.

c) Garrido, N. M.; Díez, D.; Domínguez, S.H.; García, M.; Sánchez, M.R.; Davies, S.G.; *Tetrahedron: Asymmetry* **2006**, *17*, 2183-2186.

d) Garrido, N. M.; Rubia, A. G.; Nieto, C.; Díez, D. *Synlett* **2010**, *2010*, 587-590.

e) Nieto, C. T.; Gonzalez-Nunez, V.; Rodríguez, R. E.; Diez, D.; Garrido, N. M. *European Journal of Medicinal Chemistry* **2015**, *101*, 150-162.

6. Daly, J.W.; Takuma, T.; Habermahl, G.; Karle, I.L.; Witkop, B. *Liebigs Ann. Chem*. **1969**, *729*, 198.

7. a) Garrido, N.M.; García, M.; Díez, D.; Sánchez, M.R.; Sanz, F.; Urones, J. G. *Organic Letters* **2008**, *10*, 1687-1690.

b) Garrido, N. M.; García, M.; Sánchez, M. R.; Díez, D.; Urones, J. G. *Synlett* **2010**, *3*, 387-390.

c) Garrido, N. M.; García, M.; Sánchez, M. R.; Díez, D.; Sanz F.; Urones, J. G. *Tetrahedron: Asymmetry* **2011**, *22*, 872-880.

8. a) Mann, J.; Davidson, R. S.; Hobbs, J. B.; Banthorpe, D. V.; Harborne, J. B. "*Natural Products: Their Chemistry and Biological significance*" Longman, U. K. **1996**.

b) Leete, E.; Mueller, M. E. *J. Am. Chem. Soc*. **1982**, *104*, 6440-6444.

c) Kumar, S. P.; Nagaiah, K.; Chorghade, M. S. *Tetrahedron Lett.* **2006**, *47*, 7149-7151.

9. Bentley, K. W, *Natural product reports*, **2006**, *23*, 444-463.

10. Sulzer, D., Sonders, M. S., Poulsen, N. W., & Galli, A, *Progress in neurobiology*, **2005,** *75*, 406-433.

11. a) Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833-2891;

b) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron: Asymmetry* **2012**, *23*, 1111-1153.

c) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron: Asymmetry* **2017**, *28*, 1842-1868.

12. a) Motherwell, W. B.; Crich, D. "*Free Radical Chain Reactions in Organic Synthesis*" Best Synthetic Methods, AP. **1992**.

b) Jarvis, B. B.; Yount, J. B. *J. Org. Chem*. **1970**, *35*, 2081.

c) Tada, M.; Akinaga, S.; Okabe, M. *Bull. Chem. Soc. Jpn*. **1982**, *55*, 3939-3940.

13. Gawronska, K. Gawronski, J. Walborsky, H. M. *J. Org. Chem*. **1991**, *56*, 6, 2193-2197.

14. Buckmelter, A. J. Kim, A. I. Rychnovsky, S. D. *J. Am. Chem. Soc*. **2000**, *122*, 9386-9390.

15. Newcomb, M. Park, S. U. *J. Am. Chem. Soc*. **1986**, *108*, 4132-4134.